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Escape of DNA from a Weakly Biased Thin Nanopore: Experimental Evidence for a Universal Diffusive Behavior

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We report experimental escape time distributions of double-stranded DNA molecules initially threaded halfway through a thin solid-state nanopore. We find a universal behavior of the escape time distributions consistent with a one-dimensional first passage formulation notwithstanding the geometry of the experiment and the potential role of complex molecule-liquid-pore interactions. Diffusion constants that depend on the molecule length and pore size are determined. Also discussed are the practical implications of long time diffusive molecule trapping in the nanopore.

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Understanding the statistical dynamic behavior of linear polymers in solution is of fundamental importance. For free polymers the scaling theories of de Gennes [1] and the dynamic models of Rouse and Zimm [2–4] provide a basic framework. The addition of geometric constraints on the molecule motion requires further inquiry [5]. One important case is a long linear polymer threaded through a small nanopore in a thin membrane [6,7]. Recent interest in this problem has been motivated by nanopore-based DNA sequencing [8–10].

The most straightforward experimental studies of this molecular motion have focused on measuring the time it takes for a charged polymer to completely pass from one side of a nanopore to the other under a dominant electrophoretic influence from a strong dc voltage bias applied across the pore. The complete passage or “translocation” time for each molecule is measured from its transient influence on the pore’s electrical conductance. Measurements on an ensemble of molecules provide information on the deterministic and stochastic physics at play [7,11–15].

Here instead we probe the escape time of precaptured double-stranded DNA (dsDNA) molecules in a solid state pore when the electrophoretic role of the voltage bias relative to the diffusive processes is, by contrast, minimal. Ideally, we seek a universal behavior expected when the parts of the molecule outside the pore are in near thermal equilibrium and strong stick-slip chemical interactions between the molecule and the pore surface are absent. (Motion of single-stranded DNA in tight-fitting biological nanopores [16–18] is believed to be subject to these interactions [18,19]). We also explore this situation when a small electrophoretic perturbation is applied. We show that both diffusive and drift observations can be modeled by a simple analytical approach.

A schematic of the experiment is shown in Fig. 1(a), and the experimental procedure in Fig. 1(b). First, the average translocation time t_{trans} of DNA molecules is measured for a voltage bias V that captures, threads, and passes

molecules quickly through the nanopore. This information is then used to initialize diffusion-drift experiments by capturing molecules at the voltage bias V but then subsequently reducing the bias to a small value ΔV at time $t_{\text{init}} = t_{\text{trans}}/2$ after a molecule has entered the pore at $t = 0$ and been threaded halfway through. We call this time-dependent initializing bias voltage V_{init} and the corresponding current I_{init} . The molecule then undergoes a diffusive motion with a small component of drift induced by ΔV . The eventual escape of a molecule from the pore is detected by monitoring (with a lock-in amplifier) a small in-phase ac current I_{ac} induced by an ac bias voltage V_{ac} applied across the pore. When the molecule leaves the pore this current abruptly changes, enabling its escape time t_{esc} to be determined. Figure 1(b) illustrates the definitions of V_{init} , I_{init} , t_{trans} , t_{init} , t_{esc} , and I_{ac} together with their relationship to the position of the molecule with respect to the pore.

Two distinct experimental results are reported here. The first shows the effect of the small voltage biases ΔV on t_{esc} for 10 kbp (kilo-base-pair) dsDNA molecules in a 15 nm diameter pore. In the second experiment the length and ΔV dependence of t_{esc} are presented for several DNA lengths in a 5 nm pore.

Data from the single-length, 10 kbp nominal length dsDNA measurements in a ≈ 15 nm diameter pore are shown in Fig. 2. The electrolyte was 100 mM KCl (10 mM tris, 1 mM EDTA) at pH 10. The pore was fabricated by electron beam drilling [20] in an 80 nm thick silicon nitride membrane [21]. With $V = 100$ mV, the average translocation time of unfolded molecules [7,14] was $309 \pm 6 \mu\text{s}$, with a standard deviation from this average of $45 \pm 5 \mu\text{s}$. The capture and initialization of a typical unfolded molecule are shown in Fig. 2(a). Figure 2(b) shows how t_{esc} is identified from a step in the resistive component of the current I_{ac} . V_{ac} was 5 mV at 20 kHz. Escape time distributions were built up from measurements on many molecules, as shown in Fig. 2(c) for 135 individual escapes at $\Delta V = 0.04$ mV. A total of

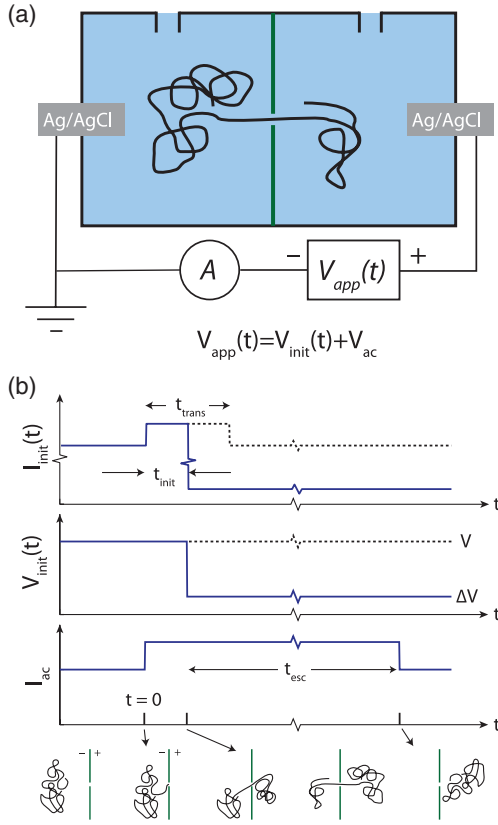


FIG. 1 (color). (a) Schematic of the experiment. (b) Time sequence of electronic signals, with molecule-pore configuration at various stages of the capture, initialization, and escape processes.

1599 unfolded events were used to build the distributions from which Fig. 2(d) is derived. The t_{esc} distributions are very sensitive to small values of ΔV , as seen in Fig. 2(d). The average escape time $\langle t_{\text{esc}} \rangle$ vs ΔV is sharply peaked around $\Delta V = 0$ with a FWHM $\approx 550 \mu\text{V}$. The average escape time is experimentally found to be insensitive to a V_{ac} amplitude increase at least up to 15 mV, or a reduction in frequency down at least to 10 kHz, indicating that the high frequency probe is not influencing the physics being measured.

The inset in Fig. 3 displays $\langle t_{\text{esc}} \rangle$ vs ΔV for DNA of nominal lengths 23.46, 10, and 6 kbp in a nanopore of diameter ≈ 5 nm in 100 mM KCl at pH 10. V_{ac} was 10 mV at 20 kHz. These results were derived from a total of 1169 unfolded events collected at various values of ΔV . The value of $\langle t_{\text{esc}} \rangle$ at $\Delta V = 0$ increases with molecule length and the ΔV width (as denoted by colored horizontal lines) narrows. The main plot in Fig. 3 shows that when ΔV is scaled inversely by the molecule length, and t_{esc} is scaled by the appropriate length-dependent time scale, the $\langle t_{\text{esc}} \rangle$ vs ΔV data collapse onto a single universal curve. We now proceed to discuss a simple model that describes this universal behavior.

We deduce the t_{esc} distributions from a one-dimensional Smoluchowski drift-diffusion equation [22,23]. This

equation describes the evolution of the probability $P(x, x', t)dx$ that a threaded molecule with position x' in the pore at $t = 0$ will be found between x and $x + dx$ after time t . For a molecule of length L , $x = 0$ and $x = L$ are the positions where either end of the molecule just escapes from the pore. For the data presented here the initial position is $x' \approx L/2$ when the diffusion process starts. The t_{esc} distributions are given by the sum of the probability fluxes $f_0(x', t)$ and $f_L(x', t)$ out of each boundary ($x = 0$ and $x = L$), with $f_{0,L}(x', t) = \pm D[\partial P / \partial x]_{x=0,L}$, where D is the diffusion constant. This function obeys an equation adjoint to the Smoluchowski equation [24],

$$\frac{\partial f_{0,L}(x', t)}{\partial t} = \frac{F(x')}{\gamma} \frac{\partial f_{0,L}(x', t)}{\partial x'} + D \frac{\partial^2 f_{0,L}(x', t)}{\partial x'^2}$$

$$f_0(0, t) = \delta(t); \quad f_0(L, t) = 0; \quad f_L(0, t) = 0; \quad f_L(L, t) = \delta(t), \\ f_0(x', 0) = 0 \quad (x' > 0); \quad f_L(x', 0) = 0 \quad (x' < L) \quad (1)$$

where $F(x')$ is the net force on the region of the molecule inside the nanopore and γ is a drag coefficient. We take γ independent of x' and linked to the diffusion constant D by the fluctuation-dissipation relation $D = k_B T / \gamma$. This assumption is only risky near the very end of the escape process [25]. $F(x')$ consists of an entropic contribution [5,19,23] and an electrophoretic force from ΔV acting on the effective charge of the molecule. The use of the entropic force relies on the assumption that the parts of the molecule outside the nanopore are in equilibrium with the fluid. For a 10 kbp molecule, for example, the longest thermal relaxation time, or Zimm time, is about 16 ms [4], which is much shorter than the measured $\langle t_{\text{esc}} \rangle$ of 140 ms shown in Fig. 2(d). The force derived from the voltage bias is $\sigma \Delta V$, where σ is an “effective” linear charge density of the DNA [12,14,26]. Using $\nu = 0.59$ as the Flory exponent arising from excluded-volume interactions, the net force is then [19,22]

$$F(x') = \sigma \Delta V - \nu \frac{k_B T}{L} \frac{1 - 2 \frac{x'}{L}}{\frac{x'}{L} (1 - \frac{x'}{L})}. \quad (2)$$

We do not include forces due to strong chemical or physical adsorption interactions between the molecule and the pore’s surface. We assume they are small due to the strong electrostatic repulsion between the negatively charged DNA and negatively charged pore surface [27] at the high pH and low electrolyte concentration used in the experiments.

The distribution function relevant to the experiment is $f(x', t) = f_0(x', t) + f_L(x', t)$ because molecules escape from both sides of the pore. We also note from the experiments that t_{trans} is not sharp and is distributed with a standard deviation relative to the mean of about 14%. This arises from the distribution of molecule configurations during the initial capture [14,28]. This width causes x' to have a small spread around $L/2$ in the experiments. We introduce a Gaussian distribution for the spread in x' : $w(x') = (2\pi\sigma'^2)^{1/2} \times \exp[-(x - L/2)^2 / (2\sigma'^2)]$, with $\sigma' = 0.14(L/2) = 0.07L$.

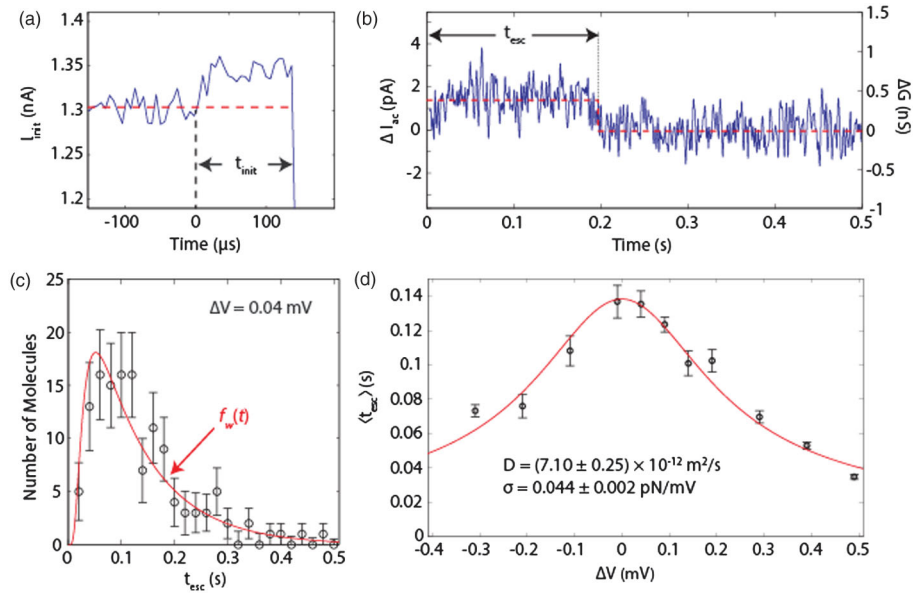


FIG. 2 (color). Capture and escape data for 10 kbp dsDNA. (a) I_{init} for a characteristic molecule before turning off V at $t = t_{\text{init}}$. The horizontal dashed line is the average open pore dc current. (b) I_{ac} for the event shown in (a). The molecule escapes the pore at $t = t_{\text{init}} + t_{\text{esc}}$. (c) Escape time distribution for $\Delta V = 0.04$ mV. Error bars based on Poisson statistics. The solid line is the theoretical t_{esc} distribution described in the text. (d) Dependence of $\langle t_{\text{esc}} \rangle$ on ΔV . The solid line is the best fit prediction for $\langle t_{\text{esc}} \rangle$ from the model described in the text.

The t_{esc} distribution function to compare with the experimental data is then

$$f_w(t) = \int_0^L w(x') f(x', t) dx' \quad (3)$$

and $\langle t_{\text{esc}} \rangle = \int_0^\infty t f_w(t) dt$. The near coincidence of solid and dashed curves in Fig. 2(c), which include and exclude this spread, respectively, shows it has little effect on the parameters determined with the model.

The solid line in the histogram in Fig. 3 is obtained from Eq. (3) using a numerical solution to Eqs. (1) and (2). The undetermined parameters required to describe all the experimental t_{esc} distributions are the diffusion constant D , the molecule's effective linear charge density σ , and a small systematic experimental voltage offset (due to electronics readout and electrode potentials) from which ΔV is referenced. These are determined by a least squares fit to be $D = (7.10 \pm 0.25) \times 10^{-12} \text{ m}^2/\text{s}$, $\sigma = 0.044 \pm 0.002 \text{ pN/mV}$, and a voltage offset of $-90 \pm 9 \mu\text{V}$. In Fig. 2(d), the measured $\langle t_{\text{esc}} \rangle$ are shown along with the model predictions using these numerical values for the parameters.

The effective charge density of the DNA is reduced from the bare charge density of 0.94 pN/mV ($2 e^-/\text{bp}$) by the electrokinetic flow in the nanopore, which is induced by the charge of the DNA and the nanopore walls. In these experiments, the effective charge density is proportional to the inverse of the width of the $\langle t_{\text{esc}} \rangle$ peak in Fig. 2(d). Its value is consistent with the charge densities, previously measured at low electric fields, of 0.05 pN/mV ($0.1 e^-/\text{bp}$) in an agarose gel [29] and 0.04 pN/mV ($0.09 e^-/\text{bp}$) under

free electrophoresis [30]. These are considerably smaller than the charge density of $\sigma \approx 0.20 \text{ pN/mV}$ ($0.43 e^-/\text{bp}$) deduced from high bias translocation time [14,26] and optical force measurements [12]. This raises the intriguing possibility that the effective charge of DNA is affected by the large fields and fluid shear forces on a DNA molecule in the pore under the large voltage biases used in electrophoretic nanopore translocation experiments [31].

D is measured to be smaller than the diffusion constant of a single Kuhn length of dsDNA moving freely along its axis, which is $24 \times 10^{-12} \text{ m}^2/\text{s}$ [32]. This is expected because of the additional hydrodynamic drag from the pore and from the parts of the molecule outside the pore. These effects will be explored in the analysis of the multiple-length experiment below.

The universal behavior in Fig. 3 follows from the model above because a natural dimensionless time for this problem is $\tilde{t} = t/(L^2/4D)$. Defining the dimensionless initial position as $\tilde{x} = 2(x'/L) - 1$ and defining $\tilde{f}_{0,L}(\tilde{x}, \tilde{t}) d\tilde{t} = f_{0,L}(x', t) dt$ puts Eqs. (1) and (2) into the form

$$\begin{aligned} \frac{\partial \tilde{f}_{0,L}(\tilde{x}, \tilde{t})}{\partial \tilde{t}} &= \left(\frac{\sigma \Delta V L}{2k_B T} + \nu \frac{2\tilde{x}}{1-\tilde{x}^2} \right) \frac{\partial \tilde{f}_{0,L}(\tilde{x}, \tilde{t})}{\partial \tilde{x}} + \frac{\partial^2 \tilde{f}_{0,L}(\tilde{x}, \tilde{t})}{\partial \tilde{x}^2} \\ \tilde{f}_{0,L}(\mp 1, \tilde{t}) &= \delta(\tilde{t}) \quad \tilde{f}_{0,L}(\pm 1, \tilde{t}) = 0 \quad \tilde{f}_{0,L}(\tilde{x}, 0) = 0 \quad (\mp \tilde{x} < 1), \end{aligned} \quad (4)$$

with a dimensionless force parameter $\sigma \Delta V / (2k_B T / L)$, which is the ratio of the voltage bias force to an entropic force. This is the scaling parameter used in the horizontal

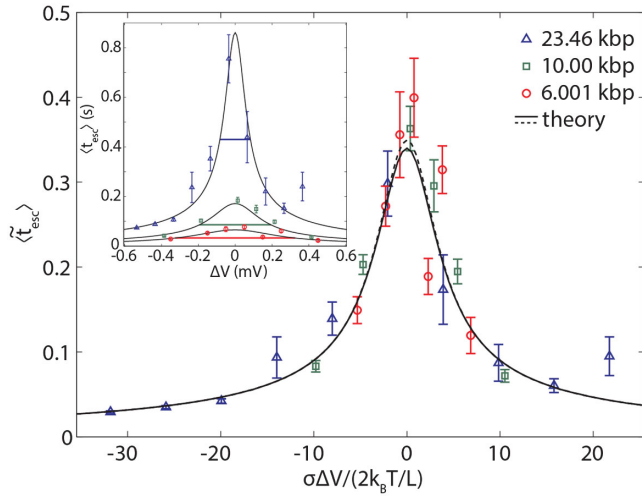


FIG. 3 (color). Length and ΔV dependence of $\langle t_{\text{esc}} \rangle$. Inset shows unscaled results from experiments. Main figure shows scaled results (see text). When scaled properly (see text) data collapse to a universal curve. The solid and dashed curves show the small effect of the spread in the initial positions.

axis in Fig. 3. The diffusion constant does not appear explicitly in Eq. (4); it is subsumed in the dimensionless time. The solutions to Eq. (4) are therefore *universal* for different lengths of molecules in the sense that they do not depend on the functional dependence of D on L .

The form of $D(L)$ can be estimated by assuming that the diffusive behavior during the escape process is determined by the parts of the molecule inside and outside the nanopore, and that the length dependence of D arises only from outside the pore. It is convenient to focus on the drag coefficient γ instead of D . γ is the sum of contributions from the parts of the molecule inside the pore, γ_p , and outside of the pore, $\gamma_L(L)$. Assuming γ_L depends on L through a power law dependence, i.e., $\gamma_L = \gamma_0(L/L_0)^{-\beta}$ we can write the total drag as $\gamma = \gamma_p + \gamma_L = \gamma_p + \gamma_0(L/L_0)^{-\beta}$. The fluctuation-dissipation theorem then yields $D^{-1} = D_p^{-1} + D_0^{-1}(L/L_0)^{-\beta}$. The reduced time becomes $\tilde{t} = t/[L^2/4D_p + (L/L_0)^\alpha L_0^2/4D_0]$, where $\alpha = 2 - \beta$ describes a D scaling behavior for the region of the molecule outside the pore. Its value is expected to be $\alpha_{\text{Zimm}} = 3\nu = 1.77$ if hydrodynamic interactions within a molecule are included, as in the Zimm model, and $\alpha_{\text{Rouse}} = 1 + 2\nu = 2.18$ if they are not, as in the Rouse model [23].

The universal curve in Fig. 3 has been obtained by least squares fitting Eq. (4) to the data from all three molecular lengths to extract D_p , D_0 , and σ from the escape time data, using $\alpha = \alpha_{\text{Zimm}} = 1.77$. For brevity, only the average escape times are shown in Fig. 3, but we emphasize that the full t_{esc} histograms are needed and used to determine the optimal parameters. The effective charge density $\sigma = 0.062 \pm 0.003$ pN/mV is larger than that obtained for the larger pore, as expected from hydrodynamic

considerations [33]. For this pore $D_p = (11.5 \pm 2.9) \times 10^{-12}$ m²/s and $D_0 = (11.4 \pm 2.5) \times 10^{-12}$ m²/s for $L_0 = 10.00$ kb.

These results indicate that for a 10 kb dsDNA molecule in a 5 nm pore about 50 percent of the drag comes from the region of the molecule inside the pore. This is qualitatively consistent with finite element calculations adapted from related previous work [26] of the hydrodynamic drag on a 2.2-nm diameter rigid rod moving through a 5-nm diameter, 30-nm long pore, which predict that approximately 67% of the measured drag comes from inside the pore. The hypothesis that the drag is hydrodynamic in origin predicts that D will increase with the diameter of the nanopore. For 10 kb molecules in the 5 nm pore, we find $D = (D_p^{-1} + D_0^{-1})^{-1} = (5.72 \pm 0.25) \times 10^{-12}$ m²/s, which is indeed smaller than $D = (7.10 \pm 0.25) \times 10^{-12}$ m²/s for the 10 kb single-length experiment in the 15 nm pore.

We have also analyzed the multiple-length data assuming that all of the drag comes from outside the pore and none from inside (i.e., $D_p \rightarrow \infty$) and fit α to the data with this assumption. A value of $\alpha = 1.90 \pm 0.04$ is obtained. This is the largest (and most unreasonable) value of α that one could extract from the data within the model used. It still dramatically contrasts with the Rouse model predictions ($\alpha = 2.18$) and with recent simulation results consistent with Rouse scaling ($\alpha \approx 2.24$ – 2.30) [25,34–36]. It also rules out $\alpha = 2$, which corresponds to the limit $D_0 \rightarrow \infty$ in which all the drag on the molecule comes from inside the pore.

We hope the first relevant experimental results presented here, and the simple analysis used, will contribute to furthering the understanding of geometrical constraints on the stochastic dynamics of polymers in nanopores. It remains to be seen what physics lurks behind our analytical model that agrees with the data yet requires the small value of α that is obtained.

Finally, we note that the slowing of the escape process by hydrodynamic interactions with the solid state pore demonstrated in this work is technologically beneficial. The absolute diffusion times are the order of hundreds of milliseconds to seconds and scale strongly with length. An unbiased nanopore by itself is thus an effective molecule trap with the diffusing molecule confined to the pore on the time scales required for more sophisticated manipulations of the molecule, such as simultaneous capture in multiple nanopores or *in situ* single-molecule chemical modification. This trapping technique has the advantages that active control is only required to capture the molecule. Also, the molecule is not tethered to a surface or bead and trapping times are longer than those achievable with active control of fast translocation [15,21]. A combined approach, in which molecules are actively recaptured as they diffuse out of the nanopore, should extend these trapping times significantly.

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